PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: KELLY, Robert M.
QI *et al.*	Art Unit: 1633 Confirmation No. 8100
Serial No. 10/804,762	CERTIFICATE OF ELECTRONIC TRANSMISSION I hereby certify that this correspondence, including listed enclosures, is being electronically transmitted in Portable Document Form (PDF) through EFS-Web via Hyper Text Transfer Protocol to the United States Patent and Trademark Office's Patent Electronic Business Center on:
Filing Date: March 19, 2004	Dated: 20 November 2007
For: *Specific Inhibition of Allorejection*	Signed: Ann - Ellie Parker

DECLARATION
Pursuant to § 1.132

The undersigned, Dr. Uwe Staerz, hereby declares as follows:

1. I received my Ph.D. in Immunology in 1986. A copy of my curriculum vitae was included with my prior declaration submitted on September 29, 2006. I am employed by Isogenis, Inc., the assignee of the above-referenced patent application and currently serve Chief Scientific Officer of the company.

2. I have read and am familiar with the disclosure in the above-referenced application and have reviewed as well the Examiner's comments in his most recent office action mailed August 23, 2007, along with the contents of U.S. Patents 5,242,687; 5,601,828; and 5,623,056 each to Tykocinski *et al.* (hereinafter "the Tykocinski patents").

3. I understand that the Examiner has a number of concerns regarding the novelty of the instantly claimed invention in light of the Tykocinski patents. Specifically, the Examiner is concerned about whether the Tykocinski patents disclose all of the features of the present claims.

4. I have scrutinized the Tykocinski patents and am certain that they do not teach at least two aspects of the present invention. First, none of the Tykocinski patents use the CD8 alpha chain alone to inhibit T cell responses, but instead only use CD8:secondary ligand constructs. Second, none of the Tykocinski patents use CD8 in conjunction with a transmembrane domain to associate the CD8 alpha chain on the cell surface, but instead use the

secondary ligand as the membrane-binding moiety. I will now explain why both of these conclusions must be drawn from the teachings of the Tykocinski patents.

5. The Tykocinski patents teach that CD8 can inhibit T cells and other cells only when it is associated with a secondary ligand, specifically, a secondary ligand that would otherwise function as a cellular activator. See, Tykocinski '828, column 3, lines 40-43; Tykocinski '056, column 3, lines 40-43; and Tykocinski '687, column 3, lines 44-48 ("Specifically, we have established that a native or genetically engineered CD8 peptide can inhibit T cells and other cells *when said CD8 peptide is associated with a second ligand* that would otherwise function as a cellular activator.") (emphasis added). The Tykocinski patents further require association with these one or more secondary ligands to achieve a pharmacologically active CD8 composition. See, Tykocinski '828, column 2, lines 25-28; Tykocinski '056, column 2, lines 25-28; and Tykocinski '687, column 2, lines 27-30 ("A pharmacologically active CD8 composition comprises a CD8 peptide *associated with one or more secondary ligands* that serve to direct CD8's inhibitory ligand activity to specific target cells.") (emphasis added). Thus the patents clearly teach the need to associate CD8 with at least one other moiety that (1) otherwise functions as a cellular activator; and (2) serves to direct CD8's activity to specific target cells.

6. The specifications proceed to provide numerous examples of such moieties for the CD8:ligand conjugates envisioned, including the following: a peptide derivative of a major histocompatibility (MHC) protein (see, e.g., Tykoicinski '828, column 2, lines 39-42; Tykocinski '056, column 2, lines 39-42; and Tykocinski '687, column 2, lines 42-45); an IgE Fc domain (see, e.g., Tykocinski '828, column 2, lines 51-52; Tykocinski '056, column 2, lines 51-52; and Tykocinski '687, column 2, lines 54-56); an unprocessed antigen (see, e.g., Tykocinski '828, column 6, line 35; Tykocinski '056, column 6, line 35; and Tykocinski '687, column 6, line 44); an Fv (antigen-binding) domain (see, e.g., Tykocinski '828, column 6, lines 59-61; Tykocinski '056, column 6, lines 59-61; and Tykocinski '687, column 7, lines 3-5); a peptidic cytokine (see, e.g., Tykocinski '828, column 7, line 1; Tykocinski '056, column 7, line 1; and Tykocinski '687, column 7, line 12); a lectin (see, e.g., Tykoicinski '828, column 7, lines 6-8; Tykocinski '056, column 7, lines 6-8; and Tykocinski '687, column 7, lines 17-19); and an anti-idiotypic mimic of another ligand (see, e.g., Tykocinski '828, column 7, lines 13-16; Tykocinski '056, column 7, lines 13-16; and Tykocinski '687, column 7, lines 26-29). As can be seen, most of the envisioned secondary ligands are peptides that are covalently linked to CD8.

7. In contrast, the present invention employs CD8 alpha without any additional moiety to bring about specific inhibition of T cell responses. Accordingly, although lacking the secondary ligand taught by Tykocinski, Applicants' expression vector nevertheless effectuates

pharmacological activities including specifically inhibiting the development of T cell responses and extending the survival of an allograft in a recipient. No such teachings can be found in (or deduced from) any of the Tykocinski patents. Instead the Tykocinski patents require association with a targeting, cellular-activating moiety to achieve pharmacological activity.

8. Turning to the second point of differentiation, the Tykocinski patents only teach using the CD8:ligand constructs to coat cells via their secondary ligands. As noted above, the Tykocinski patents teach that the secondary ligands are needed for pharmacological activity and to direct such activity to specific target cells. Indeed, the specifications provide: "A broad array of CD8:ligand combinations can be used, *each of which permits the targeting of CD8's modulatory activity to a specific subset of cells*." See, Tykocinski '828, column 2, lines 34-36; Tykocinski '056, column 2, lines 34-36; and Tykocinski '687, column 2, lines 36-39 (emphasis added). As it is the ligand that confers cell-specificity of CD8's activity, according to the Tykocinski patents, it follows that the ligand is responsible for binding to cell surfaces.

9. The entirety of the teachings from the Tykocinski patents support this conclusion. The patents discuss embodiments where CD8 peptides are linked to membrane-binding ligands, and provide a glycoinositolphospholipid-modified CD8 peptide as the preferred embodiment. Indeed, the glycoinositolphospholipid-modified CD8 peptide is the only specific example of a membrane-binding CD8 composition provided in the entire three patents. All the detailed examples, providing detailed experimental steps, exclusively discuss the glycoinositolphospholipid-modified CD8 peptide as the membrane-binding embodiment. See, Tykocinski '828, columns 8-10; Tykocinski '056, columns 8-10; and Tykocinski '687, columns 8-10 (describing production of a glycoinositolphospholipid-modified CD8 peptide); see Tykocinski '828, columns 12-13; Tykocinski '056, columns 12-13; and Tykocinski '687, columns 12-13 (describing protocol for reducing graft rejection using liposomes coated with glycoinositolphospholipid-modified CD8); see Tykocinski '828, column 15, lines 36-55; Tykocinski '056, column 15, lines 30-49; and Tykocinski '687, column 16, lines 1-14 (describing pre-treating a solid organ graft with a glycoinositolphospholipid-modified CD8 peptide composition); and see Tykocinski '828, column 15, lines 56-67 and column 16, lines 1-38; Tykocinski '056, column 15, lines 49-67 and column 16, lines 1-38; and Tykocinski '687, column 16, lines 15-63 (describing pre-treating bone marrow with a glycoinositolphospholipid-modified CD8 peptide composition). This glycoinositolphospholipid-modified CD8 is also the only specific surface-expressed embodiment mentioned in the Tykocinski patents, appearing in claim 5 of Tykocinski '687.

10. In contrast, the present invention employs the CD8 alpha chain alone in conjunction with a transmembrane domain to bring about its surface expression, as opposed to

using a secondary ligand linkage. No such teachings can be found in (or deduced from) any of the Tykocinski patents, which instead teach linking in-frame the coding sequence for the CD8 peptide with the coding sequence for a glycoinositolphospholipid-modified protein. See, e.g., Tykocinski '828, column 7, lines 46-50; Tykocinski '056, column 7, lines 45-49; and Tykocinski '687, column 7, lines 61-65.

11. In describing the production of membrane-binding CD8:ligand constructs, the Tykocinski specifications provide: "Coding sequences can be genetically engineered to create membrane-binding forms by linking, or retaining the linkage of, the coding sequences of CD8 and secondary peptide ligands to: 1) coding sequences for hydrophobic extension peptides of transmembrane proteins; or 2) coding sequences that direct glycoinositolphospholipid modification of peptides inside cells." Tykocinski '828, column 7, lines 26-33; Tykocinski '056, column 7, lines 25-32; and Tykocinski '687, column 7, lines 40-46. As I understand this teaching the modifications referred to must occur in the "secondary peptide ligand" portions of the CD8 constructs being described. First, the phrase "CD8 and secondary peptide ligands" establishes that the modifications apply to a linked construct, comprising both a CD8 peptide portion and a secondary ligand portion. Second, since the CD8 constructs rely on their secondary ligand portions to direct CD8's activity to specific target cells, it follows that the secondary ligand must be capable of "picking" the right target cells. Having a membrane-binding moiety that interacts with specific target cells readily effects this required function of the secondary ligand. Were the membrane-binding modification to occur in the CD8 portion, no such specificity could be achieved, as the Tykocinski patents nowhere teach any specific targeting activity on the part of CD8, modified or otherwise. Finally, the fact that the only membrane-binding embodiment specified in the three patents is one that binds cell membranes exclusively via its secondary ligand portion – the glycoinositolphospholipid-modifed protein portion – strongly supports my conclusion.

13. In sum, the Tykocinski patents fail to teach the use of CD8 alpha alone to inhibit T cells, as they instead teach only the use of CD8 in association with a secondary ligand to bring about pharmacological effects. Further, the Tykocinski patents fail to teach the use of a transmembrane domain with CD8 to effect surface expression, as they instead teach only the use of linked, membrane-binding ligands, not naturally associated with CD8, to target CD8's activity to specific cells. Accordingly, the invention as presently claimed remains novel in view of the Tykocinski patents.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dr. Uwe Staerz

NOV 20, 2007
Date